



Department of Health and Human Services

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Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

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By Certified Mail – Return Receipt Requested

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And by Facsimile Transmission

Warning Letter

Matthias McGuire
Acting Chief Executive Officer
Catholic Health Partners
2520 North Lakeview Avenue
Chicago, Illinois 60614

Dear Mr. McGuire:

During the period of February 8 to March 15, 2002, Lisa Hayka, an investigator with the Food and Drug Administration (FDA), conducted an inspection of Catholic Health Partners Institutional Review Committee (IRB). The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, which are published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. During the inspection the investigator copied various documents and records, including, but not limited to, IRB meeting minutes and standard operating procedures. These documents were later reviewed by the Center for Biologics Evaluation and Research, Bioresearch Monitoring Branch.

At the conclusion of the inspection a Form FDA 483, List of Observations, was issued to the IRB Chair, Robert J. O'Mara, Ph.D. We note that Dr. O'Mara stated at that time the IRB's policies and procedures would be revised, and he committed verbally to correcting all observations discussed at the time of the inspection. As of the date of this letter, we have not received any further acknowledgment or documentation to demonstrate the implementation of the promised corrective action.

Based upon the inspectional findings described in the Form FDA 483, and in the Establishment Inspection Report (EIR), as well as our subsequent review of documents collected during the inspection, we have determined that the IRB violated regulations governing the composition, operation, and responsibilities of Institutional Review Boards as published under 21 CFR 50 and 56.

These regulations are available at <http://www.access.gpo.gov/nara/cfr/index.html>. The applicable provisions of the CFR are cited for each violation listed below.

**1. Failure to prepare, maintain, and follow adequate written procedures for conducting the review of research, including periodic review.
[21 CFR §§ 56.108(a) and 56.115(a)(6)].**

A. The IRB's written procedures, as described in the Catholic Health Partners Policy ADM 313, are not adequate because they do not describe in detail the following:

- i. The document does not establish procedures to enable the IRB to conduct the activities described in 56.108(a), including initial and continuing review of research. Specifically, as cited on the Form FDA 483, the procedures do not describe how the IRB will:
 - Assure that the membership and quorum include at least one member whose primary concerns are in a non-scientific area;
 - Avoid conflict of interest in its reviews, and how the IRB will consider research proposed by IRB members;
 - Ensure that research approved by the expedited review procedure involves no more than minimal risk;
 - Determine which projects require review more often than annually;
 - Review research involving children as subjects;
 - Ensure prompt reporting to FDA, when appropriate, of any instance of serious or continuing noncompliance with FDA regulations or the requirements of the IRB, and any suspension or termination of IRB approval;
 - Determine when studies require or are exempt from IND/IDE requirements; and
 - Determine when a study involves a significant risk device.

The following examples of this violation are based on our review of documents, including the IRB's policies and procedures that were copied during the inspection. These documents did not describe how the IRB will:

- Review adverse reaction reports;
- Select members who possess the experience and expertise necessary to review specific research activities, and who are able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of conduct;
- Assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents; and
- Allow alternate members to substitute for absent IRB members.

The following specific violations are based on our review of documents, including the IRB's policies and procedures that were copied during the inspection.

- ii. The procedures described in Article VIII, Investigational Drugs for Emergency Use, are inadequate. For example, the procedures fail to state that any subsequent use of the same test article at the institution requires IRB approval, as required by 21 CFR § 56.104(c).

Additionally, the Informed Consent section for emergency use fails to list all the requirements listed under 21 CFR § 50.24 for waiving the requirement of obtaining informed consent.

- iii. Article VII, General Procedures, part A, states that IRB approval is for a specific period of time, not greater than one year. However, the procedures listed under Article VI, IRB Deliberation Process, Section 3, Post Approval Procedures, part B, allows, or appears to allow for a study to extend beyond the time initially approved by the IRB, without being subject to continuing review as long as the investigator submits a status report to the IRB. 21 CFR § 56.109(a)(2)(f) requires an IRB to conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.
- iv. Article VII, General Procedures, part C, states that the IRB may waive the requirement to provide study subjects with a copy of their signed consent document for a study involving FDA-regulated test articles. 21 CFR § 50.27(a) requires that a copy of the consent form be given to each subject, and the IRB cannot waive this requirement.
- v. Article V, IRB Review, part B, fails to state that the primary and secondary reviewers; who are selected by the IRB Chair to review a specific study and who are not IRB members, are not permitted to vote on the study they review as required by 21 CFR 56.107(f).

- B. The IRB failed to follow its written procedures for initial and continuing review. The following examples of this violation are based on our review of documents copied during the inspection, including the IRB's policies and procedures, as well as IRB meeting minutes.

- i. The IRB's procedures state the new studies will either be "Approved", "Disapproved" or "Disapproves, can resubmit". However, meeting minutes for 1999, 2000 and 2001 document that on multiple occasions the IRB failed to follow its written procedures when it granted pre-approvals, approvals pending modifications, and full approval contingent on revisions to the protocol or informed consent document.

The following example is provided for illustration, and is not a complete list.

On 1/14/00, the IRB reviewed the protocol for the study entitled -----

----- and granted full approval for one year, contingent on revisions of the protocol and consent form. Subsequent meeting minutes fail to document that the requested modifications were either submitted or prior approval was rescinded.

- ii. Article VI, IRB Deliberation Process, Section 1, Review of Application, part A, specifically requires the investigator of a research project to be present at a convened meeting to review the protocol with the IRB members, and to explain the purpose of, and need for the proposed research. The IRB commented specifically on this item in the May 12, 2000 meeting minutes, stating that the physician involved with the study should attend the IRC meeting to present their study.

However, during the period from July 1998 to January 2002, for at least 27 separate research projects, someone other than the physician involved with the study presented the proposed study to the IRB. Presenters included nurses, study coordinators, and secretaries.

- iii. Article III, Officers, Section 3, Duties of the Secretary, state the IRB Secretary is responsible for preparing the minutes of the meeting, and for acting as the Chair in his/her absence. However, on 10/12/01, 12/14/01, 11/12/99, and 12/4/98, someone other than the Secretary acted as the Chair. Additionally, on 11/12/99 and 12/4/98, the Secretary, who was not acting in the capacity of the Chair, voted on proposed research. The procedures do not grant the Secretary voting rights.

2. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one nonscientific member. [21 CFR § 56.108(c)].

- A. Meeting minutes for 4/14/00, 7/14/00, 6/8/01, 8/10/01, 10/12/01, 11/9/01, and 12/14/01 document that IRB members who were not present for the discussion of research protocols granted their proxies to other IRB members to vote on studies. The IRB does not have procedures that describe proxy voting. Further, there are no provisions in the regulations that allow for IRB members to give their proxies to other members.

In addition to the example noted above, which was cited on the Form FDA 483, the subsequent review of the meeting minutes copied during the inspection revealed the following violations:

- B. During the period of July 1998 through December 2001 the IRB convened at least 36 times. The meeting minutes for this period fail to specifically identify whether a non-scientific member was present during these convened meetings when new research proposals were approved, and when continuing review was conducted. During the FDA inspection, there were no IRB membership rosters available for this time period.
- C. On at least one occasion the IRB failed to have a quorum present when new research was reviewed and approved, and continuing review was conducted. At the 6/9/00 meeting there were only 6 of 12 members in attendance. The IRB's procedures state that a majority of the membership must be present to establish a quorum.

3. Failure to conduct continuing review of research at intervals appropriate to the degree of risk. [21 CFR § 56.109(f)].

The IRB failed to conduct continuing review of all prior approved studies on at least an annual basis. Further, the IRB failed to either suspend or terminate those studies for which annual continuing review had not been conducted. The following examples, which were cited on the Form FDA 483, are provided for illustration purposes, and are not a complete list.

- A. -----
----- Initial approval was granted on 3/30/00, but the continuing review was not conducted until 8/10/01.

The IRB minutes fail to document that this study was either suspended or terminated due to lack of continuing review.

- B. -----

-----Initial approval was granted by the IRB on 3/20/00. However, despite the fact that there were at least two separate instances of serious adverse events reported for this study within the first six months, there are no Periodic Review Forms, progress reports, or documentation of continuing review being conducted for this study in 2001 or as of May 15, 2002.

The IRB meeting minutes fail to document that this study was either suspended or terminated due to lack of continuing review.

- C. ----- Initial approval was granted on 9/8/00, but continuing review was not conducted until 12/14/01.

The IRB minutes fail to document that this study was either suspended or terminated due to lack of continuing review.

4. Failure to ensure that research is reviewed free from conflict of interest. [21 CFR § 56.107(e)].

The IRB meeting minutes fail to document that IRB members always excluded themselves from deliberation and voting on projects in which they were involved. The following examples, which were discovered during the review of meeting minutes copied during the inspection, are provided for illustration and are not a complete list.

- ----- is a member of the IRB and the clinical investigator for the study entitled -----

The meetings minutes for 10/12/01 failed to document that ----- did not vote on the study. The meeting minutes indicated that there were nine members present, with seven votes for approval and two recusals; however, the minutes did not identify which IRB members recused themselves from voting.

- The IRB meeting minutes dated 3/9/01, 6/13/01, 8/10/01, 9/14/01, and 11/9/01, failed to document that ----- either excused herself or abstained from voting during the continuing review of research projects in which she was the clinical investigator.

5. Failure to fulfill requirements for expedited review. [21 CFR § 56.110].

During the review of meeting minutes, which were copied during the inspection, for the dates 6/11/99, 8/13/99, and 9/10/99, it was noted that the Chair used the expedited review process to approve the use of investigational drugs for subjects based on "compassionate use."

The term "compassionate use" does not appear in either FDA or the Department of Health and Human Services regulations. Expedited review procedures are only to be used for certain kinds of research involving no more than minimal risk, and for minor changes in approved research; the uses described in the meeting minutes do not meet these criteria.

6. Failure to fulfill membership requirements. [21 CFR §§ 56.107(a) and (f)].

As cited on the Form FDA 483, meeting minutes for 7/14/00, 9/8/00, and 2/9/01, document individuals who were not members of the IRB substituted and voted for IRB members in their absence. The IRB does not have a list of alternate members, and the IRB procedures do not describe the appointment, function or voting rights of alternate members.

7. Failure to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR §§ 50.20, 50.25, and 50.27. [21 CFR § 56.109(b) and (c)].

- A. The IRB reviewed a safety report dated 11/9/99, for the study entitled -----

which reported on a second case of -----.

The sponsor of the study felt the adverse reaction was related to the administration of the test article, and recommended that the risk of -----
----- be included in the informed consent document. The sponsor provided specific phraseology and stated that other investigational sites had already revised the informed consent documents to include the specific reference to -----.

However, the IRB did not require the informed consent document to be revised. The IRB failed to ensure the rights, safety, and welfare of subjects by withholding important information concerning the possibility of severe neurological side effects associated with the study.

- B. The IRB approved consent forms that did not meet the requirements of 21 CFR §§ 50.25 and 50.27. For example, the consent form approved by the IRB for the protocol entitled -----

----- lacks the following required elements:

- A description of the reasonably foreseeable risks and discomforts associated with androgenic anabolic steroid therapy, including but not limited to liver cell tumors, peliosi hepatitis, decreased high-density lipoproteins, gynecomastia, insomnia, and depression;
- An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject;
- A statement noting the possibility that the Food and Drug Administration may inspect the study records;
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
- A statement of the number of subjects involved in the study.

In addition to the above items, which were cited on the Form FDA 483, during the review of documents copied during the inspection, including the IRB's policies and procedures, the following deviation from the regulations concerning consent forms was noted.

- C. The IRB's guidelines require a statement to be included in each consent document which reads in part: "In the event of injury or illness resulting from research procedures, Catholic Health Partners...Chicago, Illinois, is not responsible for provision of medical care nor for compensation of any expenses associated with such injury or illness....". This exculpatory language waives or appears to waive the subject's legal rights, and releases or appears to release the clinical investigator and the institution from liability, despite the prohibition contained in 21 CFR § 50.20.

8. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR Part § 56.115(a)(2) and (5)].

- A. The minutes of the IRB meetings are not accurate or in sufficient detail to show all actions taken by the IRB, and the vote on those actions, including the number voting for, against, and abstaining.

For example, the meeting minutes dated 2/12/99, 3/12/99, 4/9/99, 5/14/99, 6/11/99, 8/13/99, 9/10/99, and 11/12/99, do not indicate how many members voted for approval on new studies or voted on continuing review of ongoing studies.

The dates of meeting minutes listed above reflect those cited on the Form FDA 483, as well as additional dates noted during the subsequent review of meeting minutes that were copied during the inspection.

- B. The IRB failed to retain IRB membership rosters prior to 2002, and the current IRB membership roster as of May 15, 2002 does not list the Chair, the Secretary, or the non-scientific member.

The subsequent review of meeting minutes obtained during the inspection revealed the following additional deficiency:

- C. The meeting minutes for the period of July 1998 through January 2002, and the current list of "IRC Open Study Protocols" do not identify the primary and secondary reviewers assigned to review new studies as required by the IRB's written procedures.

It is important to include this information in the meeting minutes to document that the IRB reviewers do not have a conflict of interest.

This letter is not intended to be an all-inclusive list of violations. It is incumbent upon you and the IRB to not only correct the deficiencies cited on the Form FDA 483, and those described in this letter, but to also conduct a thorough review of the IRB's practices and procedures to ensure full compliance with the regulations.

Based on the deficiencies found during the inspection, as well as our subsequent review of documents collected during the inspection, we have no assurance that your IRB procedures are adequately protecting the rights and welfare of the human subjects of research. *For this reason, in accordance with 21 CFR 56.120(b)(2), and effective immediately,*

•no new subjects are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that adequate corrections have been made.

This restriction does not relieve the IRB of its responsibility for receiving and reacting to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken or plan to take to bring the procedures of your IRB into compliance with the applicable regulations. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should address each item listed, and include any documentation necessary to show that correction has been achieved. In addition, please submit a copy of the written notification from the IRB to each of the affected clinical investigators notifying them of the current restriction.

We will review your written response and determine whether the corrective actions are adequate to permit the IRB to resume unrestricted activities. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions may include, but are not limited to, the termination of all on-going studies approved by your IRB, and the initiation of regulatory proceedings for disqualification of your IRB.

Should you have any questions or comments about the contents of this letter or any aspects of the operations and responsibilities of an Institutional Review Board, you may contact: Robert L. Wesley at (301) 827-1948.

Please send your written response to:

Robert L. Wesley
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488
Telephone:(301) 827-1948

We request that you send a copy of your response to the FDA office listed below.

Sincerely,

/s/

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

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